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THE HISTOLOGICAL CHANGES IN EXPERIMENTAL DIPHTHERIA.[1]

PRELIMINARY COMMUNICATION.

By William H. Welch, M. D., *Professor of Pathology, and* Simon Flexner, M. D., *Fellow in Pathology.*

(From the Pathological Laboratory of the Johns Hopkins University and Hospital.)

The well-known observations of Oertel concerning peculiar histological changes in internal organs in human diphtheria, make it important to determine whether similar alterations occur in animals inoculated with the Klebs-Löffler bacillus of diphtheria. If such changes are found in the latter cases, they add valuable proof to the demonstration that the experimental is essentially identical with human diphtheria.

Microscopical changes in the internal organs, especially in the liver and kidney, in cases of experimental diphtheria have been observed by Löffler, Klein, Beck, and others. The fullest description thus far given of such changes is by Babes,[2] whose investigations on this point relate chiefly, also, to the liver and kidneys of rabbits. The changes in the liver observed by Babes varied in different cases. The principal lesions in this organ noted by him are swelling and degeneration of the liver cells, as well as proliferation of these cells, accumulation of leucocytes, often with fragmented nuclei (which, in some cases at least, he regards as evidence of proliferation), and of hyaline material and yellowish granular substance in the blood-vessels, and swelling and proliferation of the endothelial cells of the capillaries. In the kidneys he observed parenchymatous swelling of the epithelial cells, proliferation and desquamation of these, as well as of endothelial cells, and hyaline masses in the blood-vessels. In the spleen he found hyperplasia of the lymphatic apparatus, and in one case he speaks of numerous nuclear fragments in the venous lacunae.

Our study has been conducted with the view of ascertaining the histological changes in all of the organs of animals dead of experimental diphtheria. In the course of our work we have used guinea pigs, rabbits and kittens.

At the present time our experiments are not so complete as we wish to make them, but our results have been so uniform that we feel justified in presenting a brief preliminary account of them to the Society.

The cultures used in our work were obtained from undoubted cases of primary diphtheria occurring in Baltimore, and they were in all cases pure cultures of the Klebs-Löffler bacillus.

The inoculations were made into the subcutaneous tissue of the belly wall, a site being chosen midway between the axillary and inguinal regions. There was one exception to this rule, in the case of a kitten on which tracheotomy was performed and the inoculation made into the trachea.

Death occurred in the animals experimented upon in the following lengths of time:

Guinea pigs—shortest period, 38 hours; longest period, 5 days.
Rabbits—shortest period, 48 hours; longest period, 8½ days.
Kittens—shortest period, 43 hours; longest period, 5½ days.

[1] Reported to the Johns Hopkins Hospital Medical Society, May, 1891.
[2] Babes, Virchow's Archiv., Bd. 119, p. 468.

The *gross anatomical lesions* which we observed corresponded for the most part with those described by other investigators. At the seat of inoculation was a grayish, necrotic, pseudo-membranous focus, and surrounding this a deep red zone of varying size; underlying it the muscle of the belly wall was greatly congested.

The subcutaneous tissue on the side of inoculation was oedematous beginning at the seat of inoculation and extending over the entire side, often into the neck, and in some cases beyond the median line to the opposite side. The axillary and inguinal regions and the place immediately around the seat of inoculation were principally affected, and the oedema often assumed an exquisite gelatinous appearance.

In some cases this oedema was composed of pure yellowish serum, and in others it consisted of serum stained with blood. The subcutaneous lymph glands of the axillary, inguinal and cervical regions were hemorrhagic and swollen. The swelling affected the glands most on the side of inoculation; but the glands of the opposite side were reddened and sometimes enlarged. We would call attention to the ease with which moderate glandular enlargement in such small animals may be overlooked, unless the very small size of the normal glands be kept in mind.

The cavities of the body show alterations. In some cases the peritoneal cavity contained an excess of fluid—as much, sometimes, as five or six cc. Both the visceral and parietal layers of peritoneum were much injected, and ecchymoses were present in some cases. The mesenteric glands and retro-peritoneal glands were enlarged, and sometimes distinctly reddened.

The organs were not unaffected. The liver was congested; at times evidently fatty. In guinea-pigs, especially, the liver showed numerous macroscopic dots and lines on the surface and penetrating the substance of the organ. In a less degree this was true of kittens also. These dots varied in size from a pin-point to a pin-head; sometimes they were even larger. The lines were two mm. in length, or less. They appeared white, and did not project above the surface of the capsule.

Though the spleen was not perceptibly enlarged in all cases, yet in some it was markedly enlarged. There was considerable variation in this respect. Its color varied: in guinea-pigs there was no striking alteration, while in kittens the spleen was dark, often bluish black.

The kidneys were moist and hyperaemic.

The adrenals always showed an intense congestion, and in many instances were hemorrhagic.

The intestinal lymphatic apparatus showed interesting alterations. The agminated glands of the caecum and the ileum in guinea-pigs and kittens were abnormally prominent. They projected above the surface of the bowel, and exhibited a number of whitish points imbedded in a grayish material.

The pleural cavity contained in many cases an excess of fluid, amounting, at times, to three or four cc. The mediastinal glands were swollen and reddened, and the bronchial glands likewise. The heart appeared normal, while the lungs sometimes showed areas of congestion, and even of consolidation. The deep glands of the neck were often reddened, and the thyroids were uniformly congested, sometimes hemorrhagic.

The *microscopical study* of the organs was made in the fresh state by means of frozen sections, and, again, after hardening in different ways; alcohol, Flemming's solution and Mueller's fluid having been used. The hardened tissues were stained with various aniline dyes, hematoxylin and carmine. The tissues hardened in alcohol and stained with fuchsin or methylene blue, gave, as a rule, the most satisfactory results, other methods being useful for developing certain points.

Seat of Inoculation.—Bacilli of diphtheria were found regularly in the seat of inoculation. They were present in the gray necrotic-looking focus both free and within leucocytes. They may be absent from the oedematous fluid at a distance from this focus. Many of the leucocytes showed a fragmentation of their nuclei. Sections made from the seat of inoculation showed the bacilli in great numbers. The sections stained by means of Weigert's fibrin stain exhibited in a striking manner the bacilli and the fibrin.

The local action of the bacilli is of the most intense character. There is emigration and great destruction of leucocytes shown by disintegration of their nuclei; the fixed cells of the part have undergone a similar fragmentation, nuclei of connective tissue and muscle have succumbed, and leucocytes have wandered into these areas, many of the latter being destroyed also. There would appear to have been a proliferation of muscle nuclei in places not all of which have become fragmented.

Lymphatic Apparatus.—The lymph glands of the axillary and the inguinal regions were greatly affected. The changes in these structures are very typical.

There are hemorrhages under the capsule and into the substance of the gland. The blood-vessels here as elsewhere in the body contain a greatly increased number of leucocytes.

The cells of the gland are the seat of great changes. The principal lesions are in the lymph follicles, the lymph cords and lymph sinuses being also affected, though in less degree. Different follicles are affected in different degrees, and there are variations in different animals even of the same species. But in no instances were the lesions entirely absent.

The lesions consist of a marked alteration in the number, character, size, staining capacity and configuration of the nuclei making up the parts affected. The cell bodies are altered also, and an increased number of cells differing from the lymphoid type are found. The first thing that attracts attention is the unusual number of deeply-staining bodies in the tissue. These bodies are observed to vary in size and shape, and under a sufficiently high-power some of them are recognized as nuclear figures. They are usually, however, globular, and under a magnifying power of four hundred range from fine dust-like particles to larger particles, appearing with this power the size of a pin's head. The finer particles are often aggregated into larger globular masses, which are now free, and now enclosed in cells.

There are, again, deeply-staining particles present which show decided bizarre forms. Imperfect crescents, flask-shaped, bladder-like, whetstone, angular, and dumb-bell forms are more or less common. Occasionally, nuclei appear as if one end were drawn out and constricted into a ball-like protuberance that is being pinched off. The globular particles are, at times, grouped together with the bizarre forms into larger masses; what particularly distinguishes these bodies from the normal nuclei which remain is the intensity with which they stain.

All the chromatin particles, as before mentioned, are not within cells; indeed, as a rule, they do not occur in cells, though the number within cells varies considerably. In some glands much of this material is contained within globular cells several times larger than the lymphoid cells. In some sections these cells are observed to be present in considerable numbers, partly devoid of stained

particles, or nearly so, but usually they are full of the nuclear detritus.

In certain spots there is almost an absence of stained cells and particles. In these places it is possible to distinguish outlines of cells, then a finer granular, somewhat refractive, at times reticulated material, and here and there a deeply-stained particle. But there are always a few cells remaining that stain more or less, and among these are round cells, larger than the lymphoid cells. This portion stains with Weigert's fibrin stain in such a manner as to indicate that the granular material is largely made of fibrin or of a substance allied to fibrin.

In the lymph sinuses, especially, occurred a considerable number of round or slightly oblong cells, quite colorless in appearance, containing bodies which resemble in a striking manner red-blood-corpuscles, and these cells remind one of the red-blood-corpuscle carrying-cells of the typhoid spleen. In alcohol preparations it was impossible to determine the exact nature of the contents of these cells. Similar cells were found in the mesenteric glands and the spleen; in osmic acid preparations, on the other hand, they are shown to be red corpuscles.

An alteration similar to that just described is found throughout the lymphatic structures of the body: in the spleen, mesenteric glands, retro-peritoneal glands, intestinal lymphatic apparatus (Peyer's patches, solitary follicles, and diffused lymphatic tissue), the bronchial glands, mediastinal glands, and cervical glands. The only variation is one of degree. As far as our study has gone every gland examined has been more or less affected. The spleen is often very rich in nuclear fragments and foci of coagulation necrosis.

The cells of the *intestinal villi* in guinea pigs and rabbits and the epithelium of the intestinal mucous membrane were involved. The lesions in these structures showed a like tendency to vary in intensity. The most striking changes consisted in a fragmentation of the nuclei of cells in the villi, especially of those surrounding the central vessels (lacteals or blood-vessels), a disappearance of a large number of cells, and the presence of large round cells, similar to those described in the parts of the lymph glands most affected. These larger cells often showed a very slight staining power and shadows of cells were not uncommon. The nuclei of the epithelium were distinctly and extensively fragmented. Nuclear figures were to be seen and saprophytic bacteria were found in the necrotic tissue. These fragmented nuclei partook of the same characters as those already described and exhibited the same intense affinity for staining agents.

The Liver.—On frozen sections the dots and lines resolve themselves into smaller and larger masses of highly refractive cells, usually devoid of nuclei and retaining the outlines of liver cells. Reagents do not affect them to any great extent; acetic acid causes them to swell somewhat and to become slightly less refractive. These cells are hyaline and represent foci of dead liver cells. Besides the groups which were visible to the naked eye as lines and dots there are small groups and single cells which show the same change.

Sections of the hardened organ were studied. Those from alcohol were stained in methylene blue and eosine. By this method the areas of dead liver cells stand out clearly in red. The cells generally have well stained blue nuclei and lightly stained red cell bodies. But the hyaline cells are intensely red, either devoid of nuclei or, when a nucleus is present, it is manifestly altered. It is shrunken, often irregular in shape, and it stains differently from the nuclei generally.

Leucocytes are commonly found in such foci of dead liver cells. They are between the hyaline cells and sometimes apparently within them. There are fragments of nuclei in these places, some of which at least have been derived from the leucocytes which have wandered in.

An important change could be made out in these livers in connection with the central veins of certain lobules. Hemorrhages under the capsule were quite common, and in these lobules deep-seated hemorrhages into the tissue had taken place. These varied greatly in size, some being very small while others were quite large, involving the greater part of the lobules. It was observed that such intra-lobular hemorrhages originated in the central veins, and seemed to be due to a breach of continuity in their walls. For, when they were small a minute defect could sometimes be seen, and where they were larger a considerable rent was present in the vein wall through which the blood had escaped. The walls of these veins were quite refractive in the fresh state, and gave, after hardening, a quite characteristic staining for hyaline with picric acid.

This focal death of liver cells just described was observed in guinea-pigs and kittens especially. In rabbits, in one case in particular, there was an extensive diffuse degeneration of liver tissue. The liver was yellowish and evidently fatty, and on frozen sections it proved to be the seat of a most extensive fatty degeneration. The cells, after the tissue had been hardened in alcohol, stained very imperfectly, many not at all. The nuclei of the liver cells were in many places in a state of disintegration or fragmentation; a few, of division. The cells throughout entire lobules were affected. Leucocytes were numerous, both in the tissues and in the vessels, and many of those in the latter were fragmented.

The Kidneys.—Fresh frozen sections showed in guinea-pigs and rabbits fatty changes in the epithelium of the tubes and glomeruli. In kittens, owing to the large amount of fat in the epithelium normally, it is not easy to make out a pathological increase. Yet there would appear to be an absence of fat in the epithelium of the glomeruli and collecting tubes in the cortex under normal conditions. In some of our cases these structures contained minute fat drops. A more important change is a hyaline alteration of the glomerular capillaries and the smaller arteries. This was noticed in kittens in particular; and it often affected a few loops of a glomerulus, without involving the entire mass of capillaries. Hyaline substance was found completely filling the lumen of some capillaries.

Hardened and stained sections showed besides the hyaline change just mentioned fragmentation of the nuclei of the glomerular and tubal epithelium on a small scale, and the presence of minute deeply-staining round bodies between and in the tubal epithelium.

Adrenals.—These were generally congested, hemorrhages were often present, and in two cases the medullary cells were distinctly hyaline.

Lungs.—There were often hemorrhages under the pleura. The blood vessels of larger size are distended with blood, and the number of leucocytes in them increased. The capillaries in the walls of the alveoli are distended with blood likewise, and there are hemorrhages into the alveoli. There is an exudation into some of them consisting of leucocytes and fibrin; but the leucocytes are few in number. There are many large cells present having a round nucleus of considerable size which stains quite deeply, but not solidly, with fuchsin. These cells are present in

the areas of consolidation, and they are found also in considerable number in the nodes of the alveoli, that is, the points at which several of them come together. They are probably derived from the epithelial cells of these structures.

Fragmentation of nuclei is not a prominent feature in the lungs. It does occur, but not extensively. It was noticed in the areas of exudation, where it affects the nuclei of the large round cells as well as the leucocytes. Then it is seen in the epithelial lining of the larger bronchi, and in those bronchi that contain leucocytes fragments of nuclei are present in their lumina amid the exudation.

The *heart* was the seat of a fatty degeneration, more or less intense, in nearly every case. In many of them every muscle fibre seemed to have undergone a minute fatty metamorphosis. In others the process was less general.

Another change was noticed in the nuclei of the *muscle* fibres in certain cases. It consisted of a fragmentation similar to that in other parts.

The muscles adjoining the lymphatic glands of the axillary and inguinal regions showed degenerative changes. There was necrosis of muscle fibres and wandering in of large numbers of leucocytes, a myositis being the result.

Cultures were made from the blood, liver, kidney, and spleen of these animals with negative results in every instance.

THE RELATION OF THE PSEUDO-DIPHTHERITIC BACILLUS TO THE DIPHTHERITIC BACILLUS.

By A. C. Abbott, M. D., *Assistant in Bacteriology and Hygiene, Johns Hopkins Hospital.*

(*From the Pathological Laboratory of the Johns Hopkins University and Hospital.*)

(Read before the Johns Hopkins Hospital Medical Society, May 18th, 1891.)

In a contribution recently made by Professor Welch and myself upon the etiology of diphtheria[1] it was stated that in eight cases of true diphtheria examined by us we had failed to find any evidence that would lead us to believe that there existed in the organisms which had produced the disease any appreciable variation in the degree of their virulence toward susceptible animals. Attention was also called to the fact that we had failed to detect in any of these cases the organism known as the pseudo-diphtheritic bacillus.

In the eight cases examined by us, some of which were of the severe type while others were comparatively mild, we found constantly the organism described by Löffler and, as was stated, it was impossible to make out definitely any variation in their pathogenic properties.

Since the publication of that paper our studies in this direction have been continued and recently two cases have been brought to our notice, which may serve to shed some light upon the question under discussion. These cases represented clinically that group of affections of the pharynx and tonsils in which it is frequently difficult, if not impossible, to make a satisfactory diagnosis. They were mild throughout, and as may be seen from their histories presented but little that would lead one to say, positively, they were diphtheria.

The clinical histories are as follows:

Case I.—J. B., aged 59 years, was admitted to the Johns Hopkins Hospital, March 19th, 1891, suffering from shortness of breath and moderate dropsy of the legs. Examination revealed hypertrophy of the heart with high-tension pulse, albuminuria and slight oedema of the lungs. At the end of two weeks he had improved considerably, but complained of slight fever and sore throat. His voice was husky and thick and he had some difficulty and pain in swallowing food. The pillars of the fauces, the uvula and tonsils were swollen and oedematous, of an intense crimson-red color and covered with a thin, grayish-white, slightly adherent material. There was a moderate elevation of temperature, not exceeding 102° F.

He was immediately isolated.

The soreness of the throat was of short duration, and in five days every vestige of the thin membranous-looking deposit had disappeared, no extension whatever having occurred during this time. He was discharged from the Hospital on April 18th, 1891.

Case II.—P. K. was well up to Sunday, April 19th. At 3 p. m., April 19th, he began to feel badly. There was a slight chill, no shaking, fever, slept badly. He complained of sore throat and pain upon swallowing. He had considerable headache and pain through the limbs and back. There was no bleeding from the nose, no cough, no vomiting. Bowels rather constipated. His temperature on admission to the ward was 104.8° F., pulse 112, full and bounding. Respiration quick, skin hot and moist, tongue clean and dry, face flushed.

Uvula, tonsils and pillars of the fauces injected and red and covered with a yellow, pultaceous deposit.

April 21st (the day following admission), temperature 100° F., pulse 100. Patient feels much better. He has had aconite and citrate of potash every 3 hours.

April 27th. Throat still sore—a grayish-white deposit over tonsils and pillars of fauces and soft palate.

April 29th. Patient discharged well.

Microscopic examination of cover-slip preparations from the deposit in the throats of both of these patients revealed the presence of a variety of organisms, among which could be made, out the irregular curved, clubbed and spindle-forms common to the bacillus of Löffler. It may be said here that it is not safe to rely upon the microscopic examination alone of the smear preparations from these deposits, as there exist in the mouth, and particularly in the mouths of those having decayed teeth, curved and spindle-shaped bodies, the morphology of which is so like that of some of the forms common to the bacillus of Löffler that they might easily be mistaken for this organism.

In Case I cultures were made from the thin membranous deposit, the blood-serum mixture of Löffler being employed for

[1] "The Etiology of Diphtheria," by Professor Wm. H. Welch, M. D., and Alexander C. Abbott, M. D., *Johns Hopkins Hospital Bulletin*, No. 11, February and March, 1891.

the purpose. After 24 hours at 37° C., the tubes presented the appearance common to those made from an undoubted case, except, perhaps, there was an unusual number of colonies of the staphylococcus pyogenes aureus. From these blood-serum tubes there was but little difficulty in obtaining in pure culture an organism which in all of its morphological and cultural peculiarities was identical with the bacillus of Löffler, with a virulent culture of which it was constantly compared.

The colonies of this organism on nutrient glycerine agar-agar could not be distinguished from those resulting from the growth of the true organism of diphtheria.

In bouillon it presented the characteristic sedimentation and clumping without producing a diffuse clouding of the upper layers of the fluid.

On gelatine it did not produce liquefaction and its colonies were of the characteristic form.

It is non-motile.

On potato it grew in the way common to the bacillus of Löffler, as has been pointed out in the paper by Professor Welch and myself, as an invisible layer quite similar to that described for the bacillus of typhoid fever.

In short, it was not possible to differentiate by any of the culture methods at our disposal, between this organism and that described by Löffler.

The results, however, were different when this organism was inoculated into the subcutaneous tissues of guinea-pigs and kittens, both of which possess a marked susceptibility to the action of the b. diphtheriæ of Löffler.

Repeated inoculations of cultures growing on different media of this organism were negative, whereas the control animals inoculated with the cultures of the true diphtheria bacillus were positive in every case, the tissue changes being in each instance identical with those commonly following such inoculations.

From Case II the cover slips likewise presented a variety of organisms, and as in Case I a number of these were of a more or less suspicious appearance.

The cultures from this case were upon glycerine agar-agar as there was at the time no blood-serum in the laboratory. After 24 hours at 37° C., the Esmarch tubes presented a striking appearance—they contained a moderate number of colonies of different appearance, the most conspicuous being those of a bright yellow color which proved to be made up of a coccus and a few others which presented an appearance which one might conceive to be that of the bacillus of diphtheria very much magnified. They were larger, denser, and much more moist and opaque than are those of the b. diphtheriæ.

Microscopic examination, however, of cover-slip preparations from those colonies showed them to be made up of an organism, the morphology of which is strikingly like that of the organism of diphtheria. All of the different curved, pointed and spindle shapes were present as well as the large bizarre and broken involution forms so common to the true bacillus of diphtheria.

On the whole, however, these organisms are slightly larger than those of Löffler.

The growth of this organism on gelatine, agar-agar and blood-serum is so like that of the bacillus of Löffler that, excepting a greater degree of luxuriance, it is hardly possible at all times to tell the one from the other.

In bouillon there is macroscopically a tendency toward a diffuse clouding of the medium, but if a drop of this culture be examined microscopically without drying (as a hanging drop) it will be seen that the tendency throughout is to grow in minute clumps.

This organism is non-motile.

The most striking difference between this organism and the usual Löffler bacillus is its behavior toward potato.

On potato it grows with moderate rapidity as a dry, dirty brown layer which eventually covers nearly the whole surface of the potato. It is finely granular on the surface and irregularly lobulated around its borders.

This is an appearance that we have failed to find with the ordinary bacillus of Löffler and likewise is it absent from the organism which has been described for Case I.

Like the organism from Case I when inoculated into guinea-pigs it has given us negative results, whereas the control animals inoculated at the same time with the true bacillus of diphtheria died with the characteristic lesions.

In the relation of these organisms to the ordinary staining reagents I can find no difference between them and the Löffler organism. They all stain readily by the Gram method and with the other dyes commonly employed in coloring bacteria. Their appearance when stained with Löffler's alkaline methylene-blue solution is identical. If one prepares cover-slip preparations from cultures of the same age on the same medium, the one from a true diphtheria culture, the other from organisms from Case I and Case II, the only difference that one can detect is that the bacillus from Case II, which grows visibly on potato and on all other media presents a slightly coarser growth than is seen with the true diphtheria bacillus, is a little larger and presents occasionally more of the involution forms than does the Löffler organism.

The single point of distinction that can be made out between the organism obtained from Case I and the true bacillus of diphtheria is in the absence of pathogenic properties from the former, whereas in addition to this point of distinction the organism from Case II gives, as has been stated, a decided and distinct growth upon the surface of sterilized potato, an appearance which one does not see with the Löffler organism and which has thus far been absent from the organism obtained from Case I.

From these observations we feel justified in agreeing with the opinion that has been advanced by other observers, particularly Hoffmann and Roux and Yersin, that under varying conditions the virulence of the true diphtheria bacillus may be observed to fluctuate in the degree of its intensity—at one time possessing the property in a high degree, at another presenting a decided attenuation and not unfrequently a complete absence of pathogenic power.

The organism obtained from Case I we believe to be the true diphtheria bacillus which, from some unknown cause, has lost its virulence.

The organism obtained from Case II, though resembling closely the organism described by Löffler, presents a marked difference in its growth upon potato. Further investigation, however, may show, as has been the case with the typhoid bacillus, that this divergent mode of growth on potato is not a trustworthy criterion of distinction.

VENESECTION IN CARDIAC AND ARTERIAL DISEASE.

By Henri A. Lafleur, M. D., *Resident Physician Johns Hopkins Hospital.*

(Read before the Hospital Medical Society, April 21st, 1891.)

One is almost expected to offer an apology for bringing the subject of venesection before a medical society at the present day, owing to the discredit into which the practice has fallen during the last thirty years. Such an apology exists in the fact that an interest in the subject has quite recently been revived, and venesection has been discussed at meetings of various medical societies and in current medical literature. Special reference may be made to a paper by Dr. Pye-Smith, abstracted in the British Medical Journal, January 31, 1891, on "The Therapeutical Value of Venesection; its Indications and its Limits," read and discussed at a meeting of the Royal Medical and Chirurgical Society of London. In this paper were recorded nearly fifty cases in which venesection has been practised in many different forms of disease, including bronchitis, broncho-pneumonia, croupous pneumonia, miliary tuberculosis of the lungs, thoracic aneurism, valvular disease of the heart, pericarditis, Bright's disease, apoplexy and epilepsy. The writer considered the indications for venesection in the order of their importance, to be: first, cyanosis with dilatation of the right side of the heart, whether from pulmonary or from some other form of obstruction to the circulation; secondly, the intense pain of thoracic aneurism; thirdly, uraemic and prolonged epileptic convulsions. Reference was also made to bleeding in fevers and inflammatory disorders. In the discussion which followed, the opinions expressed were in the main corroborative of the conclusions reached by the writer of the paper.

Since the opening of the Johns Hopkins Hospital in May 1889, we have had occasion to practise venesection on five patients, an account of which is subjoined.

Case I.—*Thoracic Aneurism—venesection for urgent dyspnœa with cyanosis—temporary relief—death from exhaustion.*

William W., aged 73, was admitted to the Johns Hopkins Hospital on May 18, 1889. He had been ailing for some months from cough, shortness of breath and pain in the right side of the chest and right shoulder and on admission was found to present the signs of aneurism of the ascending arch of the aorta. He complained especially of shortness of breath and of intense pain over the right breast and down the right arm. With rest in bed and the use of iodide of potassium he improved slightly and the intense pain was somewhat alleviated, but at night he still suffered very much from dyspnœa and cough, for which morphia had to be used freely. On the evening of May 29th he had a more than usually severe attack of shortness of breath accompanied by marked cyanosis and distention of the cervical veins. As his heart was beating strongly and regularly, it was considered that venesection would give him at least temporary relief, and accordingly fourteen ounces of blood were withdrawn from his right arm. This afforded him temporary relief; both the cyanosis and the dyspnœa became less, and he spent a more comfortable night. Shortly after the bleeding he had a profuse perspiration. He died from exhaustion two days later. The autopsy revealed a large saccular aneurism compressing the right lung, which was the seat of a chronic interstitial pneumonia.

Case II.—*Chronic Nephritis with dilated heart—extreme cyanosis—venesection with temporary relief—death.*

Jeremiah B., aged 41, was admitted to the Johns Hopkins Hospital February 5, 1890. His illness had commenced six months before with shortness of breath, and three months later he had noticed that his legs were swollen. During November he had improved slightly, but since that time both the dropsy and the shortness of breath had gradually increased, until it had involved his abdomen and arms. He had not noticed any change in the quantity or appearance of his urine. The condition of the patient on admission was as follows: Very plethoric and stout; general anasarca; respirations a little labored, 44; pulse 108, regular; no increase in tension; slight lividity of lips and tips of fingers and ears; venules of the cheeks and nose distended. There was a diminution of the area of lung resonance in the lower thorax in front, in the axilla and behind, and the breath-sounds at both bases were enfeebled. Cardiac dulness began at the third rib, but the inferior and lateral limits could not be made out. There was gallop rhythm at the apex, a moderately intense systolic murmur in the anterior axilla with accentuation and reduplication of the second sound at the pulmonary cartilage. The abdomen was very large; but there was so much fat that it was not possible to demonstrate any ascites. The urine was diminished in amount, sp. gr. 1028, and contained albumen and fatty hyaline and granular casts. The patient was freely purged with salts and given half an ounce of the infusion of digitalis every four hours. During the next three days the urine progressively increased in amount, the dropsy was slightly diminished, and the heart-sounds became more distinct, though the pulse remained rapid. At midday January 10th, after coughing up some bloody sputum during the morning, he had a severe attack of dyspnœa, and when seen a few minutes later he was extremely cyanosed; the veins of the neck were distended; the breathing feeble and shallow, while the pulse could not be counted at the wrist. The heart-sounds were rapid and indistinct, and there was tremor and jactitation of the extremities. Venesection was deferred until 2:15 p. m., when eighteen ounces of blood were withdrawn. The relief was immediate, the breathing becoming easier, and the cyanosis disappearing almost entirely. There was no return of the cyanosis or dyspnœa, but the patient died on the morning of the next day. An autopsy could not be obtained: it is probable that there were extensive hemorrhagic infarctions in the lungs.

Case III.—*Mitral regurgitation with dilated and irregular heart—cyanosis and dyspnœa—venesection with marked relief—sudden death from syncope six days later.*

Mark W., aged 22, was admitted to the Johns Hopkins Hospital June 17, 1890. He had had three attacks of inflammatory rheumatism, the first occurring four years ago, but had not shown any symptoms of cardiac mischief until three months previous to admission, when he began to be short of breath and to have palpitation on slight exertion. He had also suffered from vertigo and slight cough; his legs had been swollen for some days, and he was passing less urine than usual. Condition on admission: Face

pale, slight blueness of finger nails, œdema of legs; there was orthopnœa, R. 27. The pulse was intermittent, 36 per minute, only two out of a series of three beats of the heart reaching the radial pulse. There was slight impairment of resonance at the base of the right lung with enfeebled breath-sounds. The whole of the left side of the chest was lifted with the cardiac systole, and there was throbbing in the neck and at the epigastrium. The apex impulse was forcible and diffused in the sixth intercostal space outside the nipple line. The area of cardiac dulluess was increased in both diameters. There was irregularity in the rhythm and intensity of the cardiac beats, a loud whiffing systolic murmur at the apex, and marked accentuation of the second sound at the pulmonary orifice. There was marked albuminuria without tube-casts. The patient was ordered sulph. strychnia, gr. $\frac{1}{10}$ ter die, and ten days later, sparteine gr. $\frac{1}{8}$ was substituted for this. There was some improvement in the pulse and the œdema partially disappeared. On July 4th there was considerable cyanosis of the hands and lips; not much dyspnœa, and free perspiration. The pulse was very small and in marked contrast to the heaving impulse in the praecordial region. The heart's action was very irregular. Fifteen ounces of blood were drawn from the left arm. On the following morning the color of the patient was much better. The pulse was 96, of fairly good volume; the heart's action only slightly irregular, and there was no longer such disproportion between the cardiac systole and the pulse. The improvement continued until six days later, when the patient died suddenly in a syncopal attack. An autopsy could not be obtained.

Case IV.—*Arterial sclerosis—cardiac hypertrophy and dilatation—venous engorgement wihh slight cyanosis—stupor and delirium—venesection—recovery.*

David B., aged 50, was admitted to the Johns Hopkins Hospital December 16, 1890, suffering from cough, shortness of breath and dropsy. His illness dated from fourteen weeks before entering the Hospital. At that time he had been seized suddenly at night with shortness of breath and cough, and latterly the dyspnœa had been constant with progressively increasing dropsy and decrease in the quantity of urine passed daily. There had also been slight transitory mental disturbance. There was no history of rheumatism or syphilis. On admission he presented the following condition: Oedema of lower extremities and of the right side of the trunk (he had been lying for some time on the right side); pulse 116, regular; tension increased; respirations 44, of the Cheyne-Stokes type. There were bronchial râles at the bases of both lungs, but no dulness. The apex beat was neither visible nor palpable, and the superficial area of cardiac dulness was not increased. There was fœtal heart rhythm at the apex, and gallop rhythm at the fourth rib. No accentuation of the aortic second-sound. The urine contained a small percentage of albumen with a few hyaline and granular casts. With the use of digitalis, free purgation with salts and an occasional hot bath, the œdema rapidly subsided and the pulse became slower and of better volume. He still suffered from dyspnœa, however, and was very restless and slightly delirious at night. On December 23rd he was not so well. His tongue was dry, his pulse more rapid and occasionally intermittent, and there was drowsiness with rambling even in the day time. There was in addition considerable venous engorgement of all the superficial veins with slight cyanosis and extension of the cardiac dulness to the right of the sternum. At 3 p. m., sixteen ounces of blood were taken from his left arm, which lessened the venous engorgement in a marked degree. He was restless until three o'clock in the morning, when he fell asleep. On the next day he was quite rational; there was still some dyspnœa, but the pulse was 96 and regular. During three days following the bleeding he passed a very large quantity of urine. On January 7th he was quite free from dropsy, his mind was quite clear, he slept and ate well, and his pulse was regular, ranging from 60–70. He was discharged on this day at his own request. Three months later he called at the hospital and stated that he felt quite well and was at work.

Case V.—*Mitral regurgitation with dilated and irregular heart—extreme cyanosis—venesection—recovery.*

John B., aged 44, was admitted to the Johns Hopkins Hospital April 13, 1891, suffering from dropsy and shortness of breath. In the autumn of 1889 he had suffered severely for three months from inflammatory rheumatism, all his larger joints having been swollen and very painful, and at the same season in 1890 he had had an attack of typhoid fever. He gave no history of venereal disease. Four weeks before his admission to the Hospital he had noticed that his feet were swollen. The dropsy increased rapidly and two weeks later he was quite short of breath, so much so that if he attempted to lie in bed he would choke. He had not complained of palpitation, his bowels were regular, and he passed about the same quantity of urine as usual. When seen shortly after his admission to the ward he was found to be cyanosed, sitting up in bed and somewhat breathless. His pulse was 90–100, small and irregularly intermittent. There was a wide area of heaving cardiac impulse, the apex beat being three fingers breadth outside the left nipple. A loud blowing systolic murmur was present at the apex and was transmitted into the left axilla. The second sound was accentuated at the left border of the sternum. The lungs were clear with the exception of a few mucous râles at the bases. There was enlargement of the liver without ascites, and considerable œdema of the lower extremities. The urine was scanty, highly colored and albuminous; it contained some hyaline and finely granular casts. A milk diet, free purgation with salts, and tr. digitalis m. xv. every 4 hours, were ordered. At midnight he was very cyanotic and breathing heavily. The radial pulse was just perceptible, only one heart-beat in every four or five being felt at the wrist. The præcordial impulse was heaving and irregular, and the heart-sounds were loud. A bleeding of eighteen ounces produced immediate relief; the dyspnœa disappeared almost entirely, the cyanosis diminished, the pulse at the wrist increased in volume and frequency, and the patient was relatively comfortable for the rest of the night. The next morning he was looking well and sitting up in bed. There was still a little shortness of breath and blueness of the lips and finger tips. The pulse was 96, of fairly good volume but still irregularly intermittent. The upper limit of the cardiac dulness was at the third rib, and transversely it extended from the right border of the sternum to the apex impulse in the sixth intercostal space. There was some engorgement of the veins at the root of the neck. The auscultatory signs of the heart and lungs were as described above, and there was a slight elevation of temperature. The digitalis was discontinued and was again given on the following day in smaller doses; and two days later strychnia and strophanthus were substituted for it. From April 15 to May 1st there was irregularity in the volume of the individual beats, but not intermittency, and the urine was free from albumen and casts. On

May 6, after having been up and about for a week, he was feeling quite well; there was no œdema, lividity or shortness of breath, and he ate and slept well. The radial pulse was 80, small, irregular and once more occasionally intermitting. There was still a marked contrast between the force of the ventricular contraction and the volume of the pulse. The physical signs were not materially different from those observed the day after the bleeding. He was discharged from the hospital on this day.

The above cases illustrate the value of bleeding as a means both of affording temporary relief from distressing symptoms due to disturbances of the circulation, and also of saving life and even restoring patients to comparative health.

There is little to be added to Dr. Pye-Smith's conclusions as regards the indications for venesection and its relative value in the various classes of cases which require its performance. Our experience has been, with one exception, limited to cases of primary cardiac or arterial disease, which are undoubtedly those in which most good may be expected from its use.

Huchard[1] advocates small bleedings from time to time in the first stages of arterial sclerosis and thinks that in this way it may be possible to lessen and even delay the evils resulting from prolonged high vascular tension. He insists particularly on the value of venesection in the later stages of the same disease when the left ventricle is no longer able to cope with the increased peripheral resistance and volume of blood, and the heart is in danger of sudden arrest. This may occur even when there is but little œdema or cyanosis, though there is usually engorgement of the right side of the heart and of the veins. In addition to its purely mechanical effect, venesection removes from the blood a considerable amount of toxic material which has accumulated in it owing to the imperfect performance of the functions of the kidneys and liver, these viscera being usually more or less affected by the general arterial sclerosis. The contra-indications to venesection in cardiac and arterial disease are few. Even when death is imminent, the rapid abstraction of some ounces of blood not infrequently saves the patient. It is obvious that when marked ascites or pleural effusion co-exists with cyanosis and distressed breathing the abdomen or the pleura should be tapped and venesection delayed until it is apparent whether either of these procedures do or do not afford relief. Large hemorrhagic infarctions of the lungs and extensive disease of the myocardium or of the coronary arteries, could such conditions be definitely ascertained, would probably be a contra-indication as even temporary relief could hardly be expected under such circumstances.

[1] Huchard: Maladies du coeur et des vaisseaux, Paris, 1889.

NOTES ON NEW BOOKS.

An Illustrated Encyclopaedic Medical Dictionary. Being a Dictionary of the Technical Terms used by Writers on Medicine and the Collateral Sciences, in the Latin, English, French and German Languages, by Frank P. Foster, M. D., Editor of the *New York Medical Journal*, with Collaborators. Vol. I. and Vol. II., with Illustrations. (*New York: D. Appleton & Co.*, 1888 and 1890.)

The scope of this great work is expressed in the title. When completed it will be the fullest and most exhaustive medical dictionary in this or any other language. The two volumes already published include words from the beginning of the alphabet to Fasay, the first volume containing 752 and the second 1544 pages.

In the preface the editor says: "The value of a dictionary seems to me to depend upon its accuracy, the convenience of its arrangement and its comprehensiveness." In each of these respects this dictionary deserves high commendation. Where different groups of subjects are assigned to a number of collaborators, as with this work, it must necessarily occur that certain groups receive fuller treatment than others. This dictionary, especially in comparison with other medical dictionaries, is particularly full in words relating to medical botany and chemistry, but fortunately these are among the terms for which one is likely to consult a dictionary. There is in some instances a lack of proportion in the treatment of the subjects, some words being accorded only brief definitions, others having attached to them short articles such as one might expect in an encyclopaedia, nor is this diversity in treatment always commensurate with the relative importance of the subjects.

So far as we have tested so difficult a matter, it seems to us that the dictionary is remarkably comprehensive, scarcely a word for which we have searched having been missing. The definitions are in general sufficiently full, clear and accurate and are often accompanied with useful illustrations. Occasionally one comes upon inaccurate or unsatisfactory definitions, as where under "cancer" it is stated that this term is "restricted by Virchow to those malignant tumors that are partly or wholly of epithelial origin," where if any man's name is to be mentioned it is Waldeyer and certainly not Virchow. Under "caseation" the process is spoken of as occurring in chronic inflammations in various parts without any reference to such inflammations being tuberculous or syphilitic, and the character of the change is not well described.

But it is hardly fair in an undertaking of such magnitude involving so great labor and attention to minute detail to pick out here and there an infrequent blemish when the work is of such general excellence and usefulness as is the present one.

This dictionary promises to be a monumental production. It is to be hoped that it will receive the hearty support of the medical profession.

W. H. W.

Surgery. A practical treatise with special reference to treatment, by C. W. Mansell Moullin, M. A., M. D. Oxon. (*P. Blakiston, Son & Co., Philadelphia*, 1891.)

The work before us, a volume of nearly 1200 pages, is designed by its author for the use of students and general practitioners.

It aims to give only an epitome of the main principles of Surgery, paying especial attention to treatment. It has accomplished its purpose, in this respect, very well. Modern surgery has made such wonderful advances in recent years, and along such diverse lines, that the older standard works have been left far in the rear.

Books upon surgery are being multiplied very rapidly in the attempt to fill this gap, and to keep abreast of the times. Of all the recent treatises upon surgery in English which have come to our notice, this one seems to possess the most merit in the particular field which it is designed to cover. The general arrangement and grouping of the various pathological conditions of and injuries to the different organs, with their treatment, under the head of each organ, is preferable to the usual methods of classification, and is to be commended.

We notice some important omissions; for instance, no mention is made in the chapter on diseases of bones, of the organization of the blood clot in bone cavities; nor indeed is this principle of the healing of wounds under the moist blood scab, referred to at all, in the article on the healing of wounds.

No mention is made of the treatment of tuberculous affections of the joints and bones by injections of iodoformized oil, now so much used.

The volume as a whole, however, is very comprehensive and complete, and shows evidence of much careful and painstaking work in its preparation. It deserves, and will undoubtedly take, a high rank among its fellows.

Erratum.

In the *Bulletin* of May-June, 1891, article of Dr. Nuttall on "Method for the Estimation of the Actual Number of Tubercle Bacilli in Tuberculous Sputum," page 70, line 13, under the heading of Decolorizer, *read* 150 parts and 50 parts *instead of* 150 cc. and 50 cc.

A PECULIAR GLIOMA (NEUROEPITHELIOMA?) OF THE RETINA.

By Simon Flexner, M. D., *Fellow in Pathology.*

(*From the Pathological Laboratory of the Johns Hopkins University and Hospital.*)

The patient, E. W., from whom the eye under consideration was removed was four months old. Five weeks before the date of enucleation it was noticed that something was wrong with the eye. At the time of the first examination the oculist found the pupil dilated, the anterior chamber shallow and the tension +.

The cornea was of a gray color, and presented an appearance as if about to break down. As the child was brought into the presence of the oculist the reflex often noticed in retinal glioma was observed.

So far as could be learned there is no history of malignant tumor in the ancestors of the child. The father drank to excess at one time, and suffered from amblyopia in consequence. This is the only record of disease of the eye in the ancestors of the patient.

Several years previous to the time this case occurred the eye of another child in the family, this one 6 months of age, was enucleated for a tumor which recurred and resulted in the death of the child.

Two years after the case just related still another child in the family, this one 4 months old, had a tumor of the eye for which the parents refused to have anything done. The disease soon invaded the brain causing, it is said, the skull to become twice the normal size before death occurred.

Two weeks after the enucleation of the eye under examination the remaining eye became the seat of a similar tumor, and for this the parents refused to submit to an operation. The child now passed from under the oculist's observation and its fate is unknown.

I am indebted to Dr. William Cheatham of Louisville, Ky., for the specimen and history, and I take this opportunity to acknowledge my obligations to him.

The entire eye was sent for examination preserved in alcohol, into which fluid it had been placed after its removal. On section of the eye the vitreous chamber was seen to be filled almost entirely with a tumor mass which was apparently attached to the retina.

The tumor measured 13 mm. in its longest axis and was 9 mm. wide, its shape being irregularly globular. Surrounding the tumor incompletely was a small quantity of vitreous humor coagulated by the alcohol, and it is estimated that the entire extent of the vitreous chamber, not occupied by the tumor mass, was 5 mm. The retina was detached, displaced and distorted.

The tumor presented on section, after hardening, an appearance of dots and lines having a grayish-white color, which were surrounded by and imbedded in a darker and more homogeneous material. The lines appeared to issue from the retinal side of the tumor and to proceed towards its free end, which closely approached, although it did not quite reach the lens. The lines seemed to have a definite direction, and to run with little or no branching until nearly the periphery of the tumor was reached, At this place the branching was seen to be much more marked. and the tumor assumed a somewhat convoluted aspect.

When examined microscopically the tumor is seen to originate in the external portion of the retina. Although it is connected with the retina throughout a considerable part of its extent it is seen to originate at a point of microscopical size situated in the external nuclear layer. This point of origin is clearly made out, owing to the peculiar constitution of the tumor, and is represented in Fig. 1, *b*. As the tumor is followed from this point to the free edge of the retina it widens out considerably, and is seen to be attached to the internal limiting membrane for a distance of 7 mm. or thereabouts. The ora serrata is not involved in the attachment.

The external nuclear layer of the retina, on either side of the origin of the tumor, shows a striking abnormality in its structure. About midway of its thickness and for a depth of several cells is a line in which the cells stain differently from the remainder of the layer. The cells of the external nuclear layer stain readily in nuclear dyes as a rule, and such is the case in this specimen, with the exception of the line of cells just mentioned. These cells stain very faintly in nuclear dyes, and whereas the normal cells show a quite solid body these have a finely granulated structure.

In following the tumor from its attachment to the internal limiting membrane inwards, it is evident that the connective tissue uniting the tumor with the internal limiting membrane is continuous at intervals with large and irregular areas of slight staining cells situated in this part of the tumor (Fig. 1.)

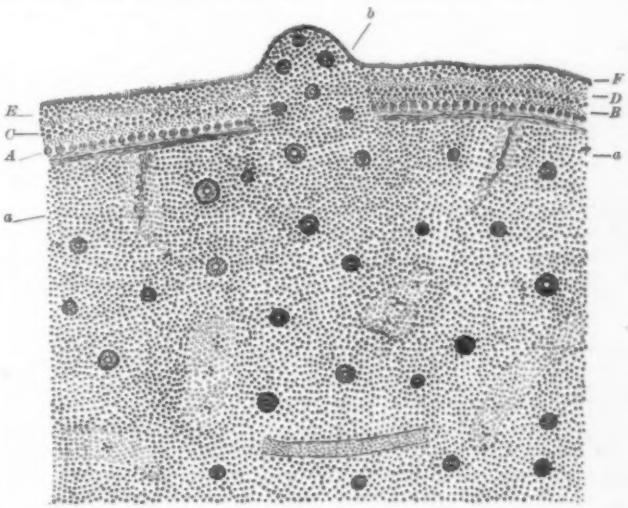

Fig. 1.

The cells composing the tumor proper may be said to consist of two principal kinds, although several kinds of cells will be described. And as the kinds of cells do not vary in the different parts of the tumor, but their particular arrangement does, it will be well to first describe the typical cells and then speak of the manner of their disposition.

The cells seen in predominating number are probably not the entire cells, but are described as such for the sake of brevity. They present the appearance of sharply stained nuclei, with scanty, often indistinct, even apparently absent cell bodies, the

contours of which appear irregular, and in favorable places, as at the edges of the sections, or in very thin, partly broken parts, thin fibre-like processes can sometimes be traced a short distance from the cell bodies. These bodies often appear as small round cells, and they will be frequently spoken of as such in this article, but we think that they have a more complicated shape and structure than this designation would imply.

These nuclei stain in the usual nuclear dyes—hæmatoxylin, carmine, magenta, iodine-green, etc., the anilines staining them more sharply than the others. They present a quite solid appearance, and notwithstanding a small amount of intercellular substance is made out by counterstaining with eosine, fuchsin or picric acid, its intimate structure did not permit of being determined in our preparations. Most probably it is partly made up of the fibre-like processes, which may be traced at times to the round cells. But owing to the manner of preserving the tissue the finer details could not be worked out.

The next most important cells in point of number are larger than the round cells, but their nuclei are not larger than the nuclei of the round cells. These large cells are usually of a columnar or rod shape, but sometimes they appear to be conical. Their nuclei are quite round, of a size not to be distinguished from the nuclei of the round cells, and they show the same affinity for staining agents as the nuclei of the round cells, and are identical in morphological structure. The bodies of the cells, on the other hand, stain very faintly, the nuclei invariably occupy the broader ends of the cells, and each cell presents opposite to the nucleus an acute terminal process. Finally, from the extremity of the cells which contains the nucleus can sometimes be seen a stalk-like prolongation which passes down between the round cells and perhaps becomes united with them, for these processes resemble those mentioned above as attached to the round cells.

Besides these there are isolated masses of cells in the tumor having a staining capacity distinct from those just mentioned. Yet, in the peculiar masses about to be described there are, mingled with the cells composing them, occasional cells, either singly or in small groups, which have the same form and staining capacity as those first described.

These peculiar cell masses exhibit the same indifference to staining agents as those observed in the external nuclear layer of the retina. Not only do they show this weak affinity for stains in general, but they present the same finely granular appearance and indistinctness as the latter.

Finally there are present in comparatively small number larger cells whose distribution is singularly irregular. These cells, which are especially to be seen in the isolated masses of light staining cells, are of variable size, and either have a perfectly homogeneous appearance without trace of nuclei, or contain blood pigment. And yet a very few cells having a coarsely granular structure, and suggesting the Mast-zellen of Ehrlich are present.

The disposition of the various cells of the tumor is important. In the first place the arrangement of the columnar cells is peculiar, striking and typical throughout the tumor, and the relation to them of the round cells is significant.

It may be stated that the columnar cells arrange themselves uniformly in one way, although an exception to this rule will be stated later. This arrangement is in the form of circles or rosettes, and it is accomplished through the juxtaposition of the sides of the cell bodies, the acute ends of the cells pointing towards the centre of the circle, while the periphery is formed by the broad ends of the cells containing the nuclei.

The rosettes vary in size, depending on the number of cells concerned in their formation, and where the acute ends of the cells are in apposition, and just before their termination a very fine although distinct membranous ring is formed, and projecting beyond this ring the delicate processes of the protoplasm of the cells forming their acute ends may be observed.

The rosettes have central lumina, the size of which also depends on the number of cells composing the circles, and they vary from almost *nil* to a considerable size. In the larger lumina, and indeed in some of the smaller, as well, a colloid or hyaline material is often seen to be present. This material is irregularly globular in shape, and a similar substance is to be seen lying in contact with the membranous ring occasionally. Indeed, it is possible to see a transformation of the delicate processes projecting beyond the ring into this material in some cases, and in these rosettes the acute processes of the cells are notably deficient.

In the rod and cone layer of the retina in this case, in parts in which the rods and cones are still visible, a similar material to that found within the lumina of the rosettes is present, and it apparently results from a gradual transformation of the rod and cone structures. For it is possible to see it in various stages of formation, and where the peculiar material is most abundant the rods and cones are either entirely absent or vestiges of them only remain.

In a few instances the peculiar round cells of the tumor were seen to occupy the lumina of certain rosettes in a way to practically exclude accidental presence.

The round cells which predominate in number over the columnar cells surround the rosettes at all places except where the rosettes are in immediate contact on one side with blood vessels as is occasionally the case. But the round cells are intimately associated with the columnar cells throughout, and the rosettes are separated from one another by the round cells. Besides the columnar cells forming the peculiar circles, a few are seen to be free among the round cells, but such single columnar cells are very rare.

It is not possible to state the exact relation of the round to the columnar cells in number, yet it may be well to remark that rosettes are quite numerous, and every field of the microscope will show a considerable number.

The cells forming the tumor, while bearing the stated relations to each other, are not disposed in one way throughout the tumor mass. At the point of the retinal attachment, and for a short distance beyond this, the cells are arranged in such a manner as to lend a quite uniform appearance to the tumor. The cells are of the two principal kinds, and are distributed everywhere alike save a few irregular masses of imperfectly staining cells corresponding to the indifferently staining cells referred to above. Where, on the other hand, the tumor is followed towards its free margin, the proper cells of the tumor take on an entirely different arrangement. With the exception of the part of the tumor adjacent to the retinal attachment, the cells are continued in the form of processes, in which there is usually a central vessel containing blood, and the thickness of the processes is made up principally of the round cells and rosettes.

This portion of the tumor is quite typical in structure. It represents the development of the tumor cells around blood vessels. It also corresponds to the lines and dots made out with the unaided eye, and it is evident that where the section passes

through the length of such a process, a line is visible to the naked eye, and where it cuts one transversely a dot is seen.

The blood vessels often show thickened walls, as has previously been pointed out by Bochert ("Untersuchungen über das Netzhaut-Gliom." Dissert. Königsberg, 1888, p. 6). In Bochert's case the coats of the vessels were infiltrated with tumor cells, a fact not true of this case.

The processes of the tumor are separated from each other by interposed masses of cells, which behave differently with staining agents than the cells of the processes. These masses of cells not only differ from the cells comprising the processes around blood vessels, but they also differ among themselves.

In the main they remind one of the peculiar qualities of the lightly staining areas in the external nuclear layer, and the more uniform portion of the tumor near the retinal attachment. But in this portion of the tumor it is possible to see all grades of difference in staining capacity, and hence in appearance between the two kinds of tumor structure. Areas are seen in which the stain taken by the nuclei and cell bodies is just perceptibly less than in the perfectly stained places, and where the cells are just beginning to lose their outline; and this is to be followed gradually into the areas in which the cells have a very faint staining capacity, and show a finely granular protoplasm. But this is not the final stage, for isolated masses of cells are seen in which a distinct cell fusion appears to be going on even to the obliteration of the individual cell outlines.

It is not always possible to decide just what cells make up these masses when the completely altered areas are examined. But when those that are least altered are first studied, it will be seen that they consist essentially of the same elements as the unaltered ones, and even in those which have changed most remnants of the peculiar structure of the undegenerated portions may be made out. An occasional rosette is still visible and remains of blood vessels are to be seen.

Besides, in the degenerated areas there is in all cases a certain number of cells which have not undergone this change. These cells are identical with the round cells of the tumor, and they lie either singly or in small groups in the altered masses. Again, in the cell processes, otherwise perfectly stained, there is to be seen in a few instances little islands of cells which have lost their staining capacity, and which presents the peculiar characteristics of the larger unstained cell masses.

It is common to find blood in these areas. This blood is not in vessels but in the tissue, and the red corpuscles only can be made out with certainty. Blood pigment is also seen and is usually contained within cells. Reference has just been made to a process of cell fusion which is seen to be taking place extensively in some of the unstained areas. It is probable that the large homogeneous cells represent this process on a smaller scale. And finally many cells in these masses are in a condition of fragmentation, this being especially true of the blood corpuscles.

Hence, these areas of unstained cell masses separate the processes of deeply staining cells around blood vessels one from another (Fig. 2). And the difference in the appearances of the two portions of the tumors, that is, at the retinal attachment, and the more peripheral portion is largely the result of the extent to which these areas are present in either part. In the neighborhood of the attachment to the retina there are very few such areas, and those present are small, consequently the tumor at this place looks quite solid and uniform. On the other hand, the peripheral portion shows large areas of unstained cells, the cell processes are strongly contrasted, and the peculiar character of this portion of the tumor results.

But this alone cannot completely explain the difference in aspect between the two portions of the tumor; for not only do the same number and extent of degenerated areas not exist in the two parts, but the blood vessels are not present in the same number or relations. In the attached portion of the tumor but few vessels are present, while they are numerous as the lens is approached.

The degeneration of a part of the tumor cells has been described in other cases of retinal glioma,[1] and indeed is not uncommon. And not only are the cells removed from the vessels the subject of such alteration, but those in immediate contact with the vessels, and in our case remains of vessels are visible in the degenerated areas.

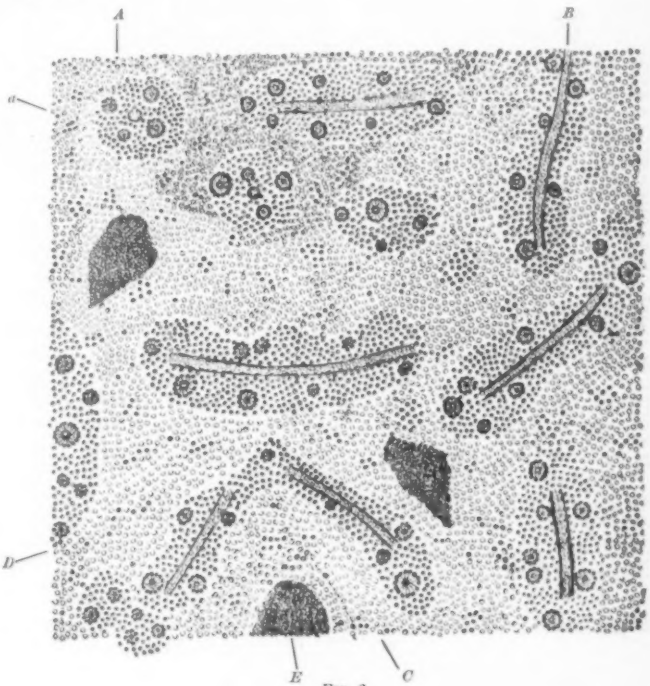

FIG. 2.

The tumor is almost purely cellular. A very few small bands of connective tissue are to be seen, and these are limited principally to the attached portion of the tumor. There was a deposit of lime salts in the degenerated portions.

From the foregoing it is evident that the tumor is to be regarded as having been originally uniform, and that the present appearance is to be explained by the degeneration of larger or smaller masses of cells. And it is to be borne in mind that a degeneration of cells similar to that seen in the various portions of the tumor is present in the external nuclear layer of the retina, from which layer the tumor takes its origin.

The consideration that glioma may have its starting point in the external nuclear layer of the retina, although affirmed by Knapp, Schweigger, Rindfleisch, Von Recklinghausen and others has been opposed by some histologists, and especially by Iwanoff (*Arch. f. Ophth.*, 1884, Bd. 15, p. 69).

[1] Bochert, *Idem.*, p. 10.

The objections urged by Iwanoff are founded on the origin of the term "glioma," for, as he states, it was introduced by Virchow to indicate a tumor having neuroglia for its basis, and so becomes a misnomer when applied to one having a more highly organized tissue for its foundation. And he urges further, that if the view of the development of the retina as taught by M. Schultze is accepted, it is necessary to regard the two most external layers of the retina, that is, the external nuclear layer and rod and cone layer, as nervous in origin. And, hence, besides the term "glioma" being out of place as applied to a structure derived from such elements, he has grave doubts of the possibility of the proliferation of them at all.

As to this last position it seems to us that it is probably going too far to deny the possibility of a proliferation of the elements of these structures. For in our case there cannot be the least doubt as to the place of origin of the tumor, that it was in the external nuclear layer, and that far from invading other layers of the retina it has not spread out in this one to any extent.

But there are other reasons for regarding this tumor as originating in the external layers of the retina. Attention has already been directed to the peculiar fact that a similar cell degeneration, to that so largely present in the tumor, is seen in the external nuclear layer; and when the cells composing the greater part of the tumor, that is, the apparently round cells, are compared with those of the external nuclear layer they will be seen to have the

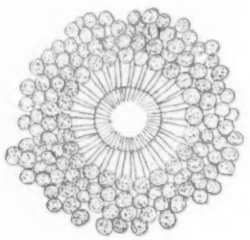

Fig. 3.

same form, size and staining affinity. Hence, on morphological grounds there is much evidence of similarity existing between the round cells of the tumor and the cells of the external nuclear layer, and when the columnar cells are examined more closely a more interesting fact becomes apparent.

It will be recalled that in the description given of the rosettes it was expressly stated that the nuclei of the cells composing them were not to be distinguished from the nuclei of the round cells, that just before the termination of the cells forming the rosettes a membranous ring was formed, and that projecting beyond this ring could often be seen fine protoplasmic processes of the cells, and further, that the nuclei of the cells always occupied the opposite and larger ends of the cells. Then surrounding these cells and in close contact with them were the round cells of the tumor.

If morphologically it is impossible to distinguish between the round cells of the tumor and the cells of the external nuclear layer of the retina, so do we consider that in each of the numerous rosettes can be seen the rod and cone layer of the retina reproduced in miniature. For it is possible to see in the membranous ring the external limiting membrane of the retina, beyond it, projecting into the lumen of the rosettes, the delicate processes of protoplasm corresponding to the rods and cones, and opposite to these the nuclei to which these processes are united. And then surrounding these nuclei, which form a part of the external nuclear layer, as it were, are the numerous round cells of the tumor which are indistinguishable from the cells of the external nuclear layer. Finally, there are to be made out, here and there, processes proceeding from the bases of the columnar cells. So that it is to be regarded that the external nuclear layer of the retina, together with the layer of rods and cones, do not show a structure materially different from that of the tumor; the sensory epithelium of the retina, with its complex arrangement, not being distinguishable from the arrangement of the cells of the tumor.

But it is not to be considered that in every rosette the matured rods and cone layer of the retina is reproduced. While this is the case in some of them others show a structure suggesting the embryonic type. In certain rosettes the processes are quite wanting, again they are present in a rudimentary form, consisting of knob-like projections, and finally they can be recognized as distinct prolongations of the kind described. A process similar to this gradual change is seen in the embryo in those animals, in which the development of the rods and cones is incomplete at birth, and it is described by Hertwig ("Lehrbuch der Entwicklungsgeschichte des Menschen und der Wirbelthiere," 1888, pp. 357 and 358) as follows: "In all vertebrates, so long as the rods and cones are not present, the inner layer of the optic cup is separated from the outer by a complete smooth contour proceeding outwards from the membrana externa. Later there appears upon this membrane numerous small, refractive knob-like processes that have been produced from the peripheral ends of the external nuclear or visual cells. These knobs consist of a protoplasmic material that stains in carmine, they extend somewhat lengthwise and form the internal segments of the rods and cones. Finally there appears on their surface the external segments, the lamellated structure of which led Max Schultze and W. Müller to compare them to cuticularizations."

Hence, this tumor is regarded as one in which the two most external layers of the retina have been reproduced, that the reproduction has taken place partly around blood vessels, that many of the tumor structures have degenerated, and the original appearance of the tumor has been much modified by this degeneration.

Is it proper to speak of this tumor as glioma? We think not. Firstly, as Iwanoff states the term was introduced to mean a tumor having its origin in neuroglia, and this tumor certainly does not have such an origin. But how then is it necessary to consider his second reason, that of the nervous structure of the two most external layers of the retina? Embryology has now shown us that these structures are not to be considered as purely nervous. It is believed (Balfour and Foster, "Elements of Embryology," 1883, p. 145; Schwalbe, "Lehrbuch der Anatomie der Sinnesorgane," 1887, p. 93) that in the course of development the retina becomes divided into an outer part corresponding to the epithelial lining of the cerebro-spinal canal, yielding what may be called the visual cells (Sehzellen, W. Müller) of the eye, *i. e.*, the cells forming the outer nuclear layer, and the layer of rods and cones attached to them, and an inner part consisting of the remaining layers of the retina, including the nerve fibres, which correspond morphologically to the substance of the brain and spinal cord. Kölliker (Entwicklungsgeschichte des Menschen und der höheren Thiere, 1879, Vol. II, p. 693) regards the rods and cones as cuticularizations of the cells destined to form the external nuclear layer, while Schwalbe (*idem.*, pp. 92 and 83) states that the retina can be divided into two parts consisting of the cerebral

portion of W. Müller (Gehirnschicht of Schwalbe) and the epithelial layer. This latter Schwalbe denominates neuro-epithelium, and it comprises the layer of external nuclei, the external limiting membrane and the layer of rods and cones, and finds its analogue in the epithelial cells of taste and of smell. Finally Shäfer ("Elements of Histology," 1885, p. 222) calls the elements the sensory or neural epithelium of the retina.

Hence, while we agree with Iwanoff that in view of the origin of the term "glioma," and in consideration of its significance, it is a misnomer to include under it tumors which spring from tissue other than neuroglia, it is clear that it cannot now, on embryological grounds, be urged that because of the peculiar nature of these structures their proliferation is hardly possible. For according to the view accepted at the present time, the layers of the retina, from which our tumor has taken its origin, is epithelial and not purely nervous in origin. Again, tumors having the highly organized tissue of the central nervous system for their foundation have been reported by Klebs ("Die Allgemeine Pathologie," 1889, p. 790).

In view of these facts, and inasmuch as record of a tumor similar to this one has not come to our notice, we propose for tumors arising from one or both of the epithelial layers of the retina the name of "neuro-epithelioma." In offering this name, and indeed in adopting the explanation which we have for the tumor under consideration, we are not unmindful of the fact that, perhaps, a closer study based on other cases under more favorable circumstances may lead to clearer views of the origin of such tumors, and hence to a more rational classification. But with the knowledge at our command at this time such a conclusion as we have arrived at is certainly not without warrant.

Aside from the interest which attaches to this tumor on account of its peculiarity of structure, we think it is quite as interesting when considered in the light of the embryonic origin of tumors in general. According to this doctrine, first propounded by Cohnheim: "In the early stage of embryonic development more cells are produced than are required for building up the part concerned, so that there remains unappropriated a quantity of cells, it may be very few in number, which, owing to their embryonic character, are endowed with a marked capacity for proliferation. . . . The new born infant brings with it into the world, not the tumor, but merely the superabundant cell-material, and from the latter, if circumstances be favorable, a tumor may grow later on." (Cohnheim, "Lectures in General Pathology," Sydenham Soc. Publications, p. 760 *et seq.*) And it is further stated that in support of this view are to be regarded the congenital nature and early development of tumors; their atypical structure, their hereditary tendency, their occurrence in situations in which, during the development of the embryo, considerable complexity exists, and their frequent primary multiplicity.

It remains to indicate how these conditions are fulfilled by the case under consideration, and what further evidence of such an origin can be derived from observations of abnormalities in development affecting the regions in which the tumor was present.

Cohnheim (*idem.*, p. 762–763) states expressly that "the occurrence of the same kind of tumor in children of the same parents may point to hereditary influence, although it has not existed in the immediate progenitors," and in the history we have referred to three cases of eye tumor in the same family, all occurring between the fourth and sixth month, and hence of congenital or early acquired nature.

It is a mere supposition, it is true, that the tumors in all three cases were similar in structure to the one just described, and yet such an inference may not be entirely unwarranted. Of their malignancy there is evidence in the occurrence of metastases and death, and the opthalmoscopic observations point to their retinal origin.

In all of the cases the tumors were multiple or early became so, and in this case, at least, both eyes were affected, although seemingly not at the same time. The atypical character of the tumor examined is striking, and admitting a histological resemblance to certain tissues of the normal retina, the morphological dissimilarity is evident and suggestive.

The complex nature and development of the retina, and the complicated series of changes in the vitreous humor and lens are to be regarded as especially predisposing to abnormalities in constitution. In the vitreous humor and lens there is a provisional set of blood vessels anastomosing with the vessels of the foetal retina. The provisional vessels should have disappeared at birth, but there are cases on record in which they or their germs have persisted. At times the arteria hyaloidea remains in a partly obliterated condition (Th. Leber, Stricker's "Manual of Histology," 1872, p. 861). Again, cells of an embryonic type have been described as present in the vitreous chamber and on the surface of the retina in post-foetal life (Balfour and Foster, "Elements of Embryology," 1883, p. 150; Kölliker, *idem.*, 1879, Vol. II, p. 666, and Iwanoff, *Archiv. f. Opth.*, Bd. XI, I, p. 155).

Finally, in the normal retina the blood vessels reach only as far forward as the external nuclear layer, but do not enter that layer. This leaves the two most external layers of the retina non-vascular. In our tumor the elements of these layers, while adjacent to blood-vessels are not, perhaps, in a more intimate relation with them than in the normal structure.

In conclusion I wish to express my indebtedness to Professor Welch and Dr. Councilman for their generous aid in describing this tumor.

Explanation of Plate.

Fig. 1. Diagrammatic representation of the retina showing origin of the tumor and section of the tumor at the retinal attachment. *A.* Ganglionic layer, layer of nerve fibres and internal limiting membrane of the retina. *B.* Internal molecular layer. *C.* Internal nuclear layer. *D.* External molecular layer. *E.* External nuclear layer. *F.* External limiting membrane and rod and cone layer. *a.* Areas of degenerated cells in the tumor at its attached border. *b.* Origin of the tumor in the external nuclear layer. This layer at the point of origin is noticed to be pushed upwards. The darker nuclei are the proper round cells of the tumor surrounding the peculiar rosettes.

Fig. 2. Representing the part of the tumor adjacent to the lens showing the processes of blood vessels and cells.

A. Process cut transversely. *a.* Blood vessel in the centre with the rosettes and round nuclei arranged around it. *B.* Process cut longitudinally showing the disposition of rosettes and round cells. *C.* Branching process. *D.* Areas of degenerated cells between the processes. Among the degenerated cells groups and single preserved round cells are to be seen. *E.* Masses of cells in a state of cell fusion.

Fig. 3. A rosette with its accompanying round cells highly magnified, The internal ring is made up of the delicate processes corresponding to the rods and cones; the middle ring represents the external limiting membrane. and the outer ring the nuclei of the rods and cones, and surrounding this are the so-called round cells of the tumor.

PROCEEDINGS OF SOCIETIES.

THE JOHNS HOPKINS HOSPITAL MEDICAL SOCIETY.

Meeting of May 4th, 1891.

Dr. OSLER in the chair. 37 members present.

Exhibition of Cases.—Dr. FINNEY.

Dr. Finney exhibited two cases of wounds healing under the blood clot; also, a case of osteo-myelitis of the femur.

Tuberculosis of the Aorta.—Dr. FLEXNER.

At the meeting of February 16th I reported on the examination of the tissues removed from the knee joint of J. W., colored, who, previous to the resection of the joint by Dr. Halsted, had had several injections of Koch's lymph.

It may be recalled that the patient had had only 9 milligrams of the tuberculine in all and that four weeks elapsed between the date of the last injection and the operation of resection, the knee having been injected with iodoformized oil in the interim.

The progress of the case following the operation was one of decline, the local wound doing fairly well, the patient dying of general miliary tuberculosis.

The autopsy, which was made by Dr. Councilman, revealed several very interesting conditions and it is deemed proper to complete the former report by briefly giving the history of the case following the operation, together with an abstract of the autopsy and the result of the histological examination of some of the tissues removed.

The joint was resected on January 23rd. On January 27th the wound was examined and found to be in the same condition as at the time of the operation. On February 1st the flap had begun to unite with the underlying tissue, but there was a space between the bones. On February 7th there is a note of the discovery of dulness at the apex of the right lung in front. February 27th the wound had improved very much, it had filled up even with the surface with healthy granulations and there was considerable stiffness between the bones. March 9th the limb could be moved as one piece from the heel. March 16th a small amount of pus was found in the anterior and outer side of the former seat of the patella. This was evacuated and the cavity injected with iodoformized oil. March 30th the lower lobe of the left lung was dull in percussion. April 3rd there was a cheesy discharge from the wound in the inner side of the knee, also through the opening in the anterior surface and from a sinus at the upper angle of the wound. All of these openings communicated with each other. They were injected with iodoformized oil. April 16th the patient died.

Excluding the rise of temperature following the operation it rose to 103° on February 25th. At this time the local condition was good. During March the temperature was below 100° as a rule and throughout April it fluctuated between 99.5° and 102°. The last week of his life it varied between 100.5° and 102°.

At autopsy the right lower extremity was 4 cm. shorter than left. Knee joint fixed, patella absent, slight amount of motion. The tissues above the joint were infiltrated with pus. The joint is united by firm ligamentous attachment at the sides. Also a certain amount of fibrous union between the opposed surfaces of the bones. The fibrous union is in the outer side and in the middle of the joint. Elsewhere there was a purulent, gelatinous looking mass between the bones.

There was an absence of tuberculous tissue on the edges of the bone forming the fibrous joint, except at the inner aspect of the femur. The joint surface presented at this place an eroded, worm-eaten appearance, which was white and caseous for an extent of 1 cm. from the surface into the bone. Below this, in the marrow of the bone, are several white, caseous points ½ to 2 mm. in diameter.

On microscopical examination it was seen that the white areas were composed of a tuberculous tissue in the form of miliary tubercles and diffuse caseous masses. The tubercles exhibit a quite active inflammatory process taking place around them, and there are numerous leucocytes in the caseous material.

In the histological examination of the bone just described we were much assisted by the employment of a method of decalcification recently recommended by Haug (Haug: "Ueber eine neue Modification der Phloroglucinentkalkungs Methode." Centralblatt für Allgemeine u. Pathologische Anatomie, Band II, p. 193). The advantages of it are that the decalcification proceeds rapidly, and the staining properties of the tissue are not affected. The solution consists of Phloroglucin, 1.0, nitric acid, 10.0, (not the fuming acid). These are mixed and warmed gently in an open dish until the reaction has ceased, and then to it are added, nitric acid, 10.0, water, 100.0, and all are mixed together. The previously hardened tissues are immersed in this, and the decalcification determined by means of a needle. As it takes place rapidly it is desirable to make the test every few minutes. When the lime salts have all been removed the tissues are washed in running water for a day before proceeding with them in the usual way.

Both lungs, but the right especially, were firmly adherent. The left parietal pleura between the adhesions was covered with a fresh fibrinous exudation. Here and there were tolerably firm tubercles in the pleura.

Left lung voluminous; surface pale. Numerous small ecchymoses on the surface. Scattered through the entire upper lobe are numerous caseous masses, some so large as to comprise a single lobule. Between these there are numerous smaller, perfectly smooth, opaque, caseous masses, which frequently form an arborescent figure. In addition, there are small cavities with caseous walls, into which the bronchi freely enter. Besides these there are smaller caseous masses with hyperaemic lung tissue around them. Caseous pus could be squeezed from the bronchi in this portion of the lung.

In the lower lobe are foci of miliary tubercles in distinct groups, all of them tolerably large and firm. In a branch of the pulmonary vein leading to the lower lobe, and close beneath the pleura, is a caseous mass firmly adherent to the vein wall, and apparently immediately beneath the intima. It is 3 cm. long, and 3 mm. in diameter. It projects into the lumen of the vein, and it is smooth over its greatest extent. At one end, however, it is roughened and apparently ulcerated.

Right lung: Vessels at base, free; bronchi, pale, contain caseous pus. A cavity in the upper lobe contains caseous material. Elsewhere small caseous masses having an arborescent arrangement, and a few small cavities. On the lower lobe are scattered miliary tubercles.

From this description it is evident that the process is an acute one, and that the affection is bronchial in origin. Microscopical examination of the caseous foci in the upper lobes show a very extensive acute tuberculous pneumonia. Caseous foci are present, in which the process is not sharply circumscribed. The surrounding lung tissue shows various conditions. The most general lesion consists of an exudation into the alveoli, which is made up, in great part, of fibrin, leucocytes and large granular cells. In the immediate vicinity of the caseous foci now under consideration this exudation, together with the alveolor walls which contain it, are undergoing a gradual necrosis.

In other parts the caseation is more sharply circumscribed, and in the surrounding lung tissue there is a considerable formation of fibrous tissue. This fibrous tissue is both within the alveoli themselves, and it also occurs as a thickening of their walls. Here and there is an extension of the caseation surrounding these larger areas, and a formation of miliary tubercles.

In the tubercles associated with this fibrous formation the caseation is solid, and there is no appearance of softening, while in the caseous foci, which are in relation with the fibrinous exudation, there are numerous pus cells. The foci are often broken down in their centres, and a small amount of granular and hyaline material is present within certain alveoli.

Hence it is evident that we have to do with two processes in the lungs: one much more acute, more recent and more rapidly advancing than the other, and it is not improbable that the acute process has been super-added to the older one. In the fibrous tissue about the firmer tubercles there are numerous miliary tubercles of a distinctly fibrous type. Tubercle bacilli were found in the specimens.

But the main interest of the case centres in a mass situated in the aorta 2½ cm. below the origin of the left subclavian artery which projected into the lumen of the vessel. This object was nodular in form, was 2½ mm. in length and 1 mm. at its highest point; it is apparently made up of several single masses, and it was pale and translucent. At the autopsy it was regarded as tuberculous. Histological examination has confirmed this supposition.

The tubercle is seated directly on the intima. The lower border is directly continuous with the surface of the aorta. The tubercle is somewhat irregular in shape, and it consists of several (3 or 4) masses containing caseous centres separated from each other by intervening connective tissue. On the outside of the caseous masses are numerous epithelioid cells and a small amount of fibrous tissue. A considerable number of leucocytes are on and within the tissue, and as the centres of the caseous masses are reached many of these are seen to have undergone fragmentation. On the aortic side there is some leucocytic infiltration just where the nodule springs from the surface of the artery, and they extend beneath the nodule for a short distance. As the middle coat of the artery is entered they disappear entirely and this coat has a perfectly normal appearance. There are no leucocytes within it, no new formation of blood vessels, nor any deviation whatever from the normal condition. The adventitia is likewise unaltered.

The surface of the nodule is apparently smooth and the greatest accumulation of leucocytes was on the surface of the highest portion of the nodules the leucocytes invading the growth, apparently, from this point. After sections were made it was not possible to state whether or not this part lay nearest the heart. At the base of the tubercle where it sprang from the aorta there was a considerable accumulation of leucocytes also. Giant cells, few in number, were on the edges of the tubercles and a few tubercle bacilli were also present.

This tubercle must have been produced from the lodgment of the tubercle bacilli on the intima under conditions which we cannot explain. There was not the slightest endarteritis in this specimen: the entire aorta was perfectly smooth excepting this tubercle and the latter has had its development in the intima. As to the leucocytes found on and in the tubercle there can be but one source of them, and that is the circulating blood.

Until recent times tuberculous affections of the arteries were not believed to occur. It has long been known that a tuberculous process in the vicinity of an artery might overtake it; but it was also known that the internal coat was extremely resistant to invasion, and hence it was considered that the intima was immune to tuberculosis.

It is now well known (Orth: Lehrbuch der Speciellen Pathologische Anatomie, Band 1, page 231) that tuberculosis of the intima occurs in the arteries of the pia, kidneys, the pulmonary artery in miliary tuberculosis, and in chronic tuberculosis (scrofula), in which latter affection the alteration appears as irregular thickenings of the intima; and finally Weigert (Virchow's Archiv, Band 88, page 360) has seen two cases of tuberculosis of the aorta itself; but they are extremely rare.

There were tubercles in this case in the liver, spleen, kidney, mesenteric and bronchial glands and peritoneum; and tuberculous ulcers in the intestine. Tubercle bacilli were found in many of the organs.

The mode of the general infection is evident. The softened tuberculous thrombus in the pulmonary vein furnished the infective emboli which disseminated the disease throughout all of the organs.

In conclusion I wish to express my indebtedness to Dr. Councilman for his assistance in describing this case.

ADDITIONAL NOTE CONCERNING THE INTRAVENOUS INOCULATION OF THE BACILLUS TYPHI ABDOMINALIS.

BY WILLIAM H. WELCH, M. D., *Professor of Pathology.*

(From the Pathological Laboratory of the Johns Hopkins University and Hospital.)

Since the publication of Dr. Blachstein's paper in the preceding number of this *Bulletin*[1] a rabbit, which had been inoculated into the ear vein with a culture of the typhoid bacillus, has been used for inoculation with another organism and typhoid bacilli have been found in the bile 128 days after the first injection. The history of this case is as follows:

March 13, 1891. A rabbit weighing 1370 grms, received by injection into the ear vein 0.5 cc. of a bouillon culture (containing 2 per cent. glucose), 48 hours old, of the typhoid bacillus. The culture was pure of the typhoid bacillus obtained originally from a single colony in a gelatine roll culture from the spleen of a case of typhoid fever. The bacillus grew invisibly on potato, and in litmus milk produced a lilac pink color with acid production and without coagulation of the milk. It was actively motile and presented all of the characteristics of the typhoid bacillus.

The rabbit's weight was taken daily for the month following the inoculation with the following result in grammes: 1370, 1240, 1250, 1240, 1290, 1290, 1300, 1335, 1275, 1250, 1240, 1220, 1260, 1290, 1290, 1270, 1280, 1370, 1320, 1340, 1330, 1220, 1170, 1180, 1175, 1210, 1240, 1270, 1360, 1285, 1310, 1290, 1305, 1280. During this time therefore the loss of weight was inconsiderable.

The animal presented no especial symptoms, and on July 18 it was used for another experiment, namely, subcutaneous inoculation with a culture of the swine plague bacillus, an organism which kills rabbits usually within 18 hours after inoculation. The rabbit died in somewhat less than 18 hours.

At the autopsy the blood and organs contain in large number the small, oval, polar-staining swine-plague bacteria, but the gall bladder and the bile present the appearances with which we were already familiar as characteristic of the presence in the gall bladder of the typhoid bacillus and which have been described in Dr. Blachstein's article. The swine-plague bacterium produces no change in the bile and does not appear in this fluid. The gall bladder is rather small and contracted, its walls grayish white, opaque and much thickened, measuring 0.75 mm. in thickness. The contents of the gall bladder consist of turbid gray, rather creamy, not viscid fluid. There is no trace of bile pigment in the bile and none visible under the microscope. The mucous membrane is smooth and thick.

[1] Blachstein—Intravenous Inoculation of Rabbits with the Bacillus Coli Communis and the Bacillus Typhi Abdominalis. *Johns Hopkins Hospital Bulletin*, July, 1891.

The liver is somewhat coarsely nodulated, and presents a number of small scars on the surface, from which narrow lines of fibrous tissue extend into the liver. These fibrous scars are probably due to the passage of cysticerci, of which several are present in the peritoneal cavity (cysticercus pisiformis). The acini of the liver are distinct. No psorosperm nodules or necrotic foci are visible.

The common bile duct has thickened walls and the same turbid gray contents as the gall-bladder. This fluid can be readily squeezed into the duodenum by pressure on the common bile duct.

The contents of the small intestine are whitish, creamy, not bile-stained, those of the caecum are greenish-yellow, normal in appearanae. The rectum contains normal-looking fecal balls.

The lungs are slightly oedematous, the spleen moderately swollen; these changes being referable to the swine-plague inoculation. There are no other lesions save the acute inflammatory oedema at the seat of swine-plague inoculation.

Cover-slip preparations of the bile show a large number (averaging about 15–30 to each field; Leitz 1-12th oil immersion) of short, rather plump bacilli, with rounded ends, resembling the typhoid bacilli. The bacilli occur both singly and in clumps. In addition there are present many well-formed cylindrical epithelial cells, not bile-stained, with nuclei, evidently desquamated from the wall of the gall-bladder. The bacilli are not motile when examined at once in a drop of bouillon; but in the course of five hours, at a temperature of 36° C., in a drop culture, they developed into actively motile bacilli. No other forms of bacteria were found in the bile. In cover-slips from the blood, liver and spleen, only the swine-plague bacteria were found, which are much shorter than the typhoid bacilli, with which they cannot be confounded.

Roll gelatine cultures from the blood, liver and spleen developed only colonies of the swine-plague bacillus, whereas similar cultures from the bile (made after thoroughly burning the surface of the gall-bladder) are pure cultures of the typhoid bacillus, no other kind of colony or organism being present in these cultures. The first tube is crowded with minute colonies; the second and third contain well distributed grayish, thin colonies, with somewhat irregular margins.

The cultures obtained from the bile were tested in every possible way to prove their identity with those of the typhoid bacillus, and in no respect do they differ from the latter. The bacillus obtained from the bile is actively motile in cultures. It grows invisibly but well upon potato; it produces acid in milk, changing the blue lilac tint of litmus milk (of amphoteric reaction) to a lilac pink without coagulating the milk. It produces no change to the naked eye in the appearance of plain milk. The bacillus is beset on all sides with flagella when stained according to Löffler's method for staining flagella.

Typhoid bacilli found in the bile at variable periods after intravenous inoculations are always devoid of motility when examined at once, but they develop into motile bacilli.

In this case, therefore, the typhoid bacilli were found in the bile of a rabbit one hundred and twenty-eight days (over four months) after intravenous injection of 0.5 cc. bouillon culture of the same organism. During this time they have produced little or no appreciable disturbance of the animal, so far as could be judged from its general appearance during life. Whether or not the animal would have eventually wasted away and died as other animals similarly affected have done cannot be said. It presented the same changes in the gall-bladder and in the bile noticed in the other rabbits which died a long time after similar inoculation, so that as soon as the gall-bladder was exposed at the autopsy I felt confident of finding the typhoid bacilli in it.

That the typhoid bacilli may make their appearance in the bile within at least 5 days after intravenous inoculation is proven by an experiment recently made by Dr. Reed in the Pathological Laboratory. The rabbit received 0.3 cc. of a bouillon culture of the typhoid bacillus in the mesenteric vein, and was killed at the end of 5 days. The bile at the autopsy was found thinner and paler than normal, but it still had a green tint. Typhoid bacilli were found both by cover-slip preparations and by cultures in the bile in considerable number.

Publications of the Johns Hopkins Hospital.

THE JOHNS HOPKINS HOSPITAL REPORTS.

Volume II, for 1890. The second volume of the Hospital Reports began in January, 1890. They will contain pathological, medical, surgical and gynecological papers and reports, details of cases, the technique of operations, etc. Subscriptions will be received for the volume, of about 500 pages, at $5. The price of the separate fasciculi will vary with their size and the number of plates they contain. The following numbers of this volume are now ready.

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